II. REMARKS

Claims 17, 19-21 and 26-35 are pending in the subject application. By this Amendment and Reply, claims 19-21, 26, 28, 29, 31, 32, 34 and 35 have been amended herein. New claim 36 has been added.

The amendments to the claims are made without prejudice or disclaimer to Applicant's right to pursue the same or similar claims in a continuation application. Additionally, the amendment of claims is not intended by Applicant as a dedication to the public of the subject matter of the claims as previously presented.

Support for amending the claims to recite in part "phenyl monophosphate" is found in Figure 6 and on page 3, lines 27 through 29. Support for additional claim amendments are noted in the context of the specific remarks below. New claim 36 is supported on page 16, lines 12 to 22 and Table 9, appearing on page 76. These amendments do not raise an issue of new matter and entry thereof is respectfully requested.

In view of the preceding amendments and the following remarks, reconsideration and withdrawal of the objections and rejections are respectfully requested.

Objections to the Specification

The Office alleged that the Sequence Listing submitted along with the Reply of March 30, 2006, was non-compliant with the requirements of 37 C.F.R. §1.821 through §1.825. Without acquiescing to the correctness of this contention, Applicant has addressed the alleged defects with the enclosure of a substitute sequence listing as a computer readable form (CRF) and accompanying paper copy of the sequence listing. A copy of the Notice to Comply is also enclosed. Applicant's undersigned attorney declares that the substitute sequence listing provided on the CRF is identical to the paper copy enclosed herewith, and that the substitute sequence listing contains no new matter. In view of the enclosed paper copy and computer readable diskette, removal of

the objection is respectfully requested. Entry of the paper copy of the sequence listing into the application file is respectfully requested.

Claim Informalities

Claims 19, 20, 21, 28, 32, 34 and 35 were objected to for alleged informalities. Claims 19, 20, 21, 32, 34 and 35 have been amended to conform the name of the product of the action of phosphoramidase on BVDU-PA to the corresponding monophosphate. Support for these amendments is found in Figure 6 and its description in the specification at page 3, lines 27 through 29. Claims 28 and 31 have been amended to correct typographical errors. In view of the amendments to claims 19-21, 28, 31, 32, 34 and 35, removal of the grounds for objection are respectfully requested.

35 U.S.C. § 101

Claims 20 was rejected under 35 U.S.C. § 101 allegedly because claimed recitation of a use without setting forth steps involved in the process results in an improper process claim. Without acceding to the correctness of the Examiner's interpretation of the statute vis a vis claim 20, Applicant has amended the claim by substituting the Examiner's suggested use of the term "administration" for the term "use". Support for the amendment is found at page 6, lines 22 through 24 and at page 66, line 29 through page 67, line 11. Removal of the grounds for rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims 20, 21, 34 and 35 were rejected under 35 U.S.C. § 112, first paragraph. The Office contends that the recitation of "assaying for cell death" is not adequately

supported. Applicant respectfully traverses the rejection. The disclosure at page 55, beginning at line 5 and continuing through line 24, details assays for cell growth inhibition. In these experiments, the cells are exposed to the compounds for 24 hours after which a redox indicator dye, alamarBlue, is added and following a 4 hour incubation, the cell culture is analyzed by fluorescence spectroscopy. When plotted on a standard curve, the data correlating concentration of the cells with fluorescence emission indicates the level at which culture growth is inhibited at the various dosages of experimental compound. Since inhibition on the single cell level implies cell death, Applicant submits that the assay for cell death as recited in the claim is supported and does not require further exposition in the claims since the details of the steps of the assay of cell death have been described in the specification as filed. Further, as taught in the specification at page 64, lines 8-28, the assay methodology referred to in the cited reference of Patterson et al (1998) also using the alamarBlue assay, describes how cytotoxicity is determined in cell lines exposed to Tomudex and 5FdUrd. This procedure is described as a screening method (line 19) as recited in the preamble of the claim. Clearly, the step of assaying for cell death is well supported and unambiguous for providing guidance for one of ordinary skill in the art to execute the method of the claims 20, 21, 34 and 35. Withdrawal of the rejection is earnestly solicited.

Claims 17, 19 and 26-33 also were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not described in the specification in a manner to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Office contends that the specification does not provide enablement for treatment of the scope of neoplastic diseases encompassed by either claim 26 or 29 or of any disease condition with multiple active ingredients as specified generically in claim 29 or specifically in claim 17. At the same time, the Office admits that the specification provides enablement, "for NB1011 in the treatment of a few specific disease conditions."

Applicant respectfully traverses noting that claims 26 and 29 require that the cancer cell whose proliferation is inhibited by the claimed method necessarily endogenously overexpresses thymidylate synthase. Conversely, cancers associated with cell proliferation which do **not** have the property of endogenously overexpressing thymidylate synthase are **not** subject to the claim. NB1011 has been disclosed to be effective for the treatment of cancer in cells based upon methods disclosed in the example on page 71 with colon cancer and in the results shown in Table 4 (page 73) for a large variety of cancer cells. Since the common property of these cell types is overexpression of thymidylate synthase, Applicant did have in his possession at the time the priority application was filed a method for treating diseases having this common characteristic. Additionally, as previously noted, the Office has not provided any objective reason why one of skill in the art would doubt efficacy of the claimed compounds against any cell which overexpresses thymidylate synthase.

Accordingly, in view of the above remarks, reconsideration and withdrawal of the grounds for rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 26 and 29 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Without repeating the grounds for the rejection, claim 26 has been amended in accordance with the Examiner's recommendation.

The Office has also rejected claim 29 based on the contention that the terms "monophosphate" and "phosphoramidate" derivative of an amino acid" are insufficiently detailed to permit the ordinary practitioner to know what particular substances are being described.

Applicant responds that there is no ambiguity with respect to having both a monophosphate diester and an aminoacyl phosphoramidate in the generic structure of claims 26 and 29. The disclosure of the specification describes both monophosphates and phosphoramidatyl derivatives of an amino acid as alternatives for the variable R^7. As illustrated in Figure 6, when the compound is an aminoacyl phosphoramidate, such as BVDU-PA (a/k/a NB 1011), the endogenous cellular phosphoamidases catalyze conversion of the compound to the corresponding monophosphate (BVDU-MP). This structure and synonomous terminology for this structure were known at the time of the filing of the priority application. Therefore, the method of contacting the cell can utilize either the phosphoramidate or monophosphate form of the claimed compound.

The Office also alleges ambiguity in claim 29 for defining a method of treating wherein two active ingredients are present but failing to define the identity of the first ingredient, thereby rendering the noted claim indefinite. Applicant traverses and notes that the method is to combined use and that the first compound is identified by its ability to inhibit thymidylate synthase activity. New claim 36 notes specific example of such compounds.

In view of the preceding amendments, reconsideration and withdrawal of the grounds for rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

Double-Patenting Rejections

The Office maintained the double patenting rejections made earlier as follows:

Claims 17, 19-21 and 26-35 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,495,553 for the reasons of record;

Claims 17, 19-21 and 26-35 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 36-39 of U.S. Patent No. 6,339,151 for the reasons of record;

Claims 17, 19-21 and 26-35 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-7 of U.S. Patent No. 6,245,750 for the reasons of record; and

Claims 17, 19-21 and 26-35 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 of U.S. Patent No. 6,683,061 for the reasons of record.

Applicant respectfully defers to the filing of a terminal disclaimer until allowable subject matter has been indicated.

The Examiner also maintained provisional rejections for obviousness-type double patenting over copending applications as follows:

Claims 17, 19-21 and 26-35 as allegedly unpatentable over claims 56-84 and 86-89 of U.S. Patent Application No. 09/782,721 for the reasons of record;

Claims 17, 19-21 and 26-35 as allegedly unpatentable over claims 15-18, 21-23 and 27-50 of U.S. Patent Application No. 09/789,226 for the reasons of record;

Claims 17, 19-21 and 26-35 as allegedly unpatentable over claims 1-36 of U.S. Patent Application No. 11/034,036 for the reasons of record;

Claims 17, 19-21 and 26-35 as allegedly unpatentable over claims 1-18 of U.S. Patent Application No. 10/051,320 for the reasons of record; and

Claims 17, 19-21 and 26-35 as allegedly unpatentable over claims 1 and 53-83 of U.S. Patent Application No. 11/034,036 for the reasons of record.

Applicant contends that since the claims in the aforementioned applications are presently under prosecution and none have been allowed, it is premature to terminally disclaim the instant claims over co-pending claims which may be amended to remove any alleged obviousness-type double patenting. Per the provisions of 37 C.F.R. §1.78 (b), conflicting claims may be canceled or amended to become patentably distinct during their prosecution in the event of issuance of the present claims. Applicant,

therefore, respectfully requests withdrawal of the rejection under the contention that conflicting claims are subjects for prosecution in the other applications rather than the present application.

Supplemental Information Disclosure Statement

Attached to this Reply is a Supplemental Information Disclosure Statement and necessary copies of references for consideration and entry into the application file. As this Supplemental Information Disclosure Statement is submitted in connection with the accompanying RCE, no additional fee is deemed necessary.

III. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition

for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: January 11, 2007

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